IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

TOIVOLA et al

Serial No. 497,813

filed 25th May, 1983

for

"NOVEL TRI-PHENYL ALKANE AND ALKENE DERIVATIVES AND THEIR PREPARATION AND USE"

D E C L A R A T I O N

I, LAURI SAKARI NIEMINEN, declare:

1. That I am a citizen of Finland of Valppakuja 4, 21360 Lieto AS, Finland. I am a Docent of Toxicology at the University of Jyvaskyla, Finland and a Doctor of Philosphy. I am the LAURI SAKARI NIEMINEN who made the Declaration dated October 31st 1984 previously filed in support of this Application.

2. The following experiments have been carried out under my supervision to compare the subacute toxicity of the known drug clomifene with that of a compound supplied to me by Farmos Group Ltd. and identified by them as 4-chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy] phenyl]-1-butene, hereinafter called compound 7.

3. Under my supervision, the toxicities of compound 7 and clomifene citrate were compared in female rats in a toxicity test as follows. The oral dose levels used were 1 mg/kg, 10 mg/kg and 100 mg/kg. The dosing took place seven days a week for a two week period. There were 5 female rats in each group.

4. The following mortalities were observed:

Control		0/5
Compound 7	1 mg/kg	1/5
"	10 mg/kg	0/5
"	100 mg/kg	1/5
Clomifene	1 mg/kg	0/5
"	10 mg/kg	0/5
"	100 mg/kg	5/5

In the test group of compound 7 at the 1 mg/kg dose level one animal died immediately after the ninth dose. The left lobe of lungs were haemorrhagic, signs of emphysema were observed in right lobes of lungs. The reason of death was intubation error.

In the test group of compound 7 at the 100 mg/kg dose level one animal died on the fourteenth test day. The autopsy performed indicated that the reason of death was acute gastric dilatation.

In the test group of clomifene at the dose level of 100 mg/kg, all five animals died during the sixth to eighth test days. The autopsies performed indicated that the reasons of death were acute gastric dilatation.

In hematological studies performed on the surviving animals no toxic changes were observed. Furthermore, no changes in the relative weight of organs and no macroscopic organ damage caused by the drugs were observed in the autopsies performed on the surviving animals.

Acute gastric dilatation is a fatal disease condition and is probably caused by the atony of the stomach. On the basis of the performed autopsies it seems evident that compound 7 and clomifene caused the death of the animals by the same mechanism. However, I conclude from the results that compound 7 has a significantly lower toxicity than clomifene. In the test group of clomifene at the dose level of 100 mg/kg all five rats died during the sixth to eighth test days but in the test group of compound 7 at the same dose level of 100 mg/kg, only one animal died, and this only occurred on the fourteenth test day.

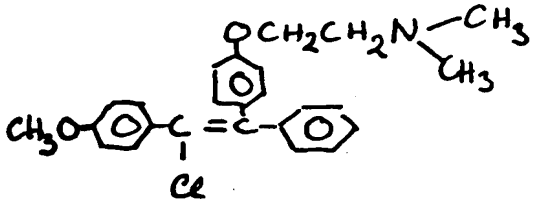
The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the Application or any Patent issuing thereon.

LAURI SAKARI NIEMINEN

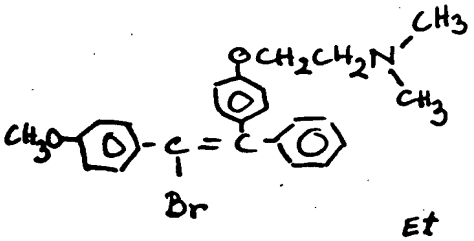
Dated this 15 day of May 1985

encl. 2

ex. 1



ex 2



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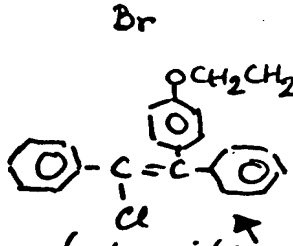
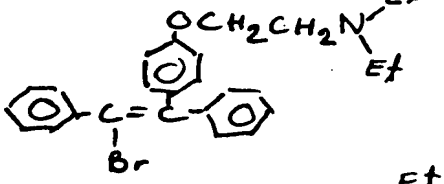


(clomifene)

ex 4



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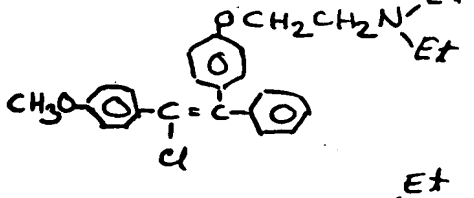

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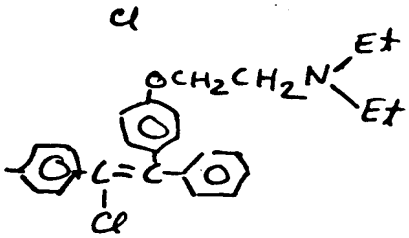

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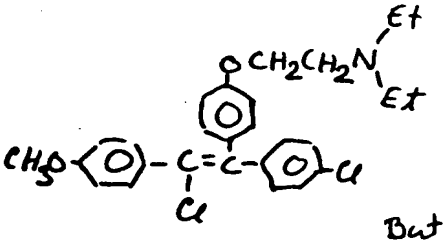

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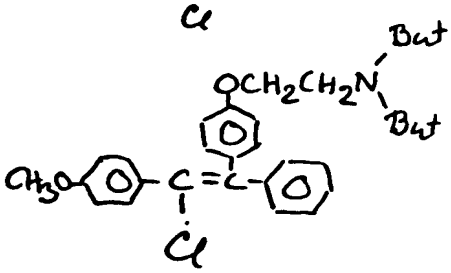

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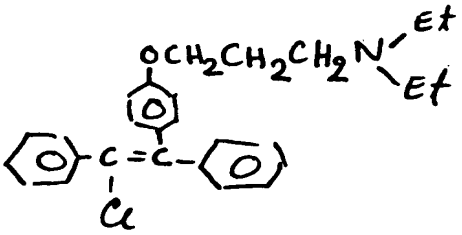

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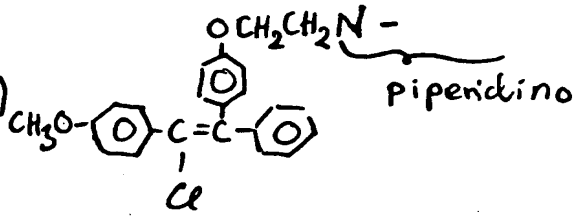

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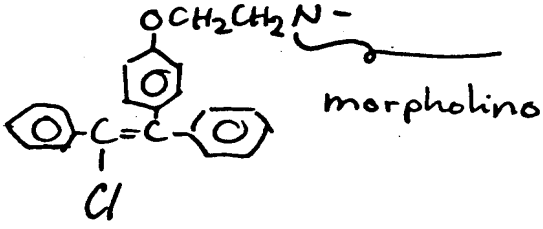

Compounds disclosed in US pat 2914563, Allen et al.